



## Tolvaptan in patients with autosomal dominant polycystic kidney disease

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**Abstract:** **BACKGROUND:** The course of autosomal dominant polycystic kidney disease (ADPKD) is often associated with pain, hypertension, and kidney failure. Preclinical studies indicated that vasopressin V(2)-receptor antagonists inhibit cyst growth and slow the decline of kidney function. **METHODS:** In this phase 3, multicenter, double-blind, placebo-controlled, 3-year trial, we randomly assigned 1445 patients, 18 to 50 years of age, who had ADPKD with a total kidney volume of 750 ml or more and an estimated creatinine clearance of 60 ml per minute or more, in a 2:1 ratio to receive tolvaptan, a V(2)-receptor antagonist, at the highest of three twice-daily dose regimens that the patient found tolerable, or placebo. The primary outcome was the annual rate of change in the total kidney volume. Sequential secondary end points included a composite of time to clinical progression (defined as worsening kidney function, kidney pain, hypertension, and albuminuria) and rate of kidney-function decline. **RESULTS:** Over a 3-year period, the increase in total kidney volume in the tolvaptan group was 2.8% per year (95% confidence interval [CI], 2.5 to 3.1), versus 5.5% per year in the placebo group (95% CI, 5.1 to 6.0;  $P<0.001$ ). The composite end point favored tolvaptan over placebo (44 vs. 50 events per 100 follow-up-years,  $P=0.01$ ), with lower rates of worsening kidney function (2 vs. 5 events per 100 person-years of follow-up,  $P<0.001$ ) and kidney pain (5 vs. 7 events per 100 person-years of follow-up,  $P=0.007$ ). Tolvaptan was associated with a slower decline in kidney function (reciprocal of the serum creatinine level,  $-2.61$  [mg per milliliter] $(-1)$  per year vs.  $-3.81$  [mg per milliliter] $(-1)$  per year;  $P<0.001$ ). There were fewer ADPKD-related adverse events in the tolvaptan group but more events related to aquaresis (excretion of electrolyte-free water) and hepatic adverse events unrelated to ADPKD, contributing to a higher discontinuation rate (23%, vs. 14% in the placebo group). **CONCLUSIONS:** Tolvaptan, as compared with placebo, slowed the increase in total kidney volume and the decline in kidney function over a 3-year period in patients with ADPKD but was associated with a higher discontinuation rate, owing to adverse events. (Funded by Otsuka Pharmaceuticals and Otsuka Pharmaceutical Development and Commercialization; TEMPO 3:4 ClinicalTrials.gov number, NCT00428948.)

**BACKGROUND:** Acidosis and transplantation are associated with increased risk of bone disturbances. This study aimed to assess bone morphology and metabolism in acidotic patients with a renal graft, and to ameliorate bone characteristics by restoration of acid/base homeostasis with potassium citrate. **METHODS:** This was a 12-month controlled, randomized, interventional trial that included 30 renal transplant patients with metabolic acidosis ( $S-[HCO(3)(-)] <24$  mmol/L) undergoing treatment with either potassium citrate to maintain  $S-[HCO(3)(-)] >24$  mmol/L, or potassium chloride (control group). Iliac crest bone biopsies and dual-energy X-ray absorptiometry were performed at baseline and after 12 months of treatment. Bone biopsies were analyzed by in vitro micro-computed tomography and histomorphometry, including tetracycline double labeling. Serum biomarkers of bone turnover were measured at baseline and study end. Twenty-three healthy participants with normal kidney function comprised the reference group. **RESULTS:** Administration of potassium citrate resulted in persisting normalization of  $S-[HCO(3)(-)]$  versus potassium chloride. At 12 months, bone surface, connectivity density, cortical thickness, and cortical porosity were better preserved with potassium citrate than with potassium chloride, respectively. Serological biomarkers and bone tetracycline labeling indicate higher bone turnover with potassium citrate versus potassium chloride. In contrast, no relevant changes in bone mineral density were detected by dual-energy X-ray absorptiometry. **CONCLUSIONS:** Treatment with potassium citrate in renal transplant patients is efficient and well tolerated for correction

of metabolic acidosis and may be associated with improvement in bone quality. This study is limited by the heterogeneity of the investigated population with regard to age, sex, and transplant vintage.

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## ORIGINAL ARTICLE

# Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

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## ABSTRACT

**BACKGROUND**

The course of autosomal dominant polycystic kidney disease (ADPKD) is often associated with pain, hypertension, and kidney failure. Preclinical studies indicated that vasopressin  $V_2$ -receptor antagonists inhibit cyst growth and slow the decline of kidney function.

**METHODS**

In this phase 3, multicenter, double-blind, placebo-controlled, 3-year trial, we randomly assigned 1445 patients, 18 to 50 years of age, who had ADPKD with a total kidney volume of 750 ml or more and an estimated creatinine clearance of 60 ml per minute or more, in a 2:1 ratio to receive tolvaptan, a  $V_2$ -receptor antagonist, at the highest of three twice-daily dose regimens that the patient found tolerable, or placebo. The primary outcome was the annual rate of change in the total kidney volume. Sequential secondary end points included a composite of time to clinical progression (defined as worsening kidney function, kidney pain, hypertension, and albuminuria) and rate of kidney-function decline.

**RESULTS**

Over a 3-year period, the increase in total kidney volume in the tolvaptan group was 2.8% per year (95% confidence interval [CI], 2.5 to 3.1), versus 5.5% per year in the placebo group (95% CI, 5.1 to 6.0;  $P<0.001$ ). The composite end point favored tolvaptan over placebo (44 vs. 50 events per 100 follow-up-years,  $P=0.01$ ), with lower rates of worsening kidney function (2 vs. 5 events per 100 person-years of follow-up,  $P<0.001$ ) and kidney pain (5 vs. 7 events per 100 person-years of follow-up,  $P=0.007$ ). Tolvaptan was associated with a slower decline in kidney function (reciprocal of the serum creatinine level,  $-2.61$  [mg per milliliter] $^{-1}$  per year vs.  $-3.81$  [mg per milliliter] $^{-1}$  per year;  $P<0.001$ ). There were fewer ADPKD-related adverse events in the tolvaptan group but more events related to aquaresis (excretion of electrolyte-free water) and hepatic adverse events unrelated to ADPKD, contributing to a higher discontinuation rate (23%, vs. 14% in the placebo group).

**CONCLUSIONS**

Tolvaptan, as compared with placebo, slowed the increase in total kidney volume and the decline in kidney function over a 3-year period in patients with ADPKD but was associated with a higher discontinuation rate, owing to adverse events. (Funded by Otsuka Pharmaceuticals and Otsuka Pharmaceutical Development and Commercialization; TEMPO 3:4 ClinicalTrials.gov number, NCT00428948.)

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\*The investigators and the members of the study committees of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**A**UTOSOMAL DOMINANT POLYCYSTIC KIDNEY disease (ADPKD) is the most common monogenic kidney disease and the fourth leading cause of end-stage kidney disease in adults worldwide.<sup>1,2</sup> It results in the progressive development of kidney cysts, kidney pain, hypertension, and, ultimately, kidney failure. Effective treatment for ADPKD has been lacking.

Studies of animal models implicate the antidiuretic hormone arginine vasopressin and its second messenger adenosine-3',5'-cyclic monophosphate (cAMP) as promoters of kidney-cyst cell proliferation and luminal fluid secretion. The suppression of vasopressin release by means of high water intake, genetic elimination of vasopressin, and vasopressin V<sub>2</sub>-receptor blockade all reduce the cyst burden and protect kidney function.<sup>3-9</sup> Such preclinical studies justify studying the effects of tolvaptan, a vasopressin V<sub>2</sub>-receptor antagonist,<sup>10</sup> in human ADPKD. Tolvaptan is approved for the treatment of dilutional hyponatremia (in various countries) or volume overload in heart failure (in Japan).

In 3-year, open-label clinical trials involving 63 patients with ADPKD as compared with historical controls, tolvaptan slowed the increase in total kidney volume (1.7% vs. 5.8% per year,  $P < 0.001$ ) and the decline in the estimated glomerular filtration rate (GFR;  $-0.71$  vs.  $-2.1$  ml per minute per 1.73 m<sup>2</sup> of body-surface area per year,  $P = 0.01$ ).<sup>11</sup> Limitations of these studies included the small number of patients, noncontemporary controls, and unmatched ethnic groups. Here we report the results of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial, a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial.<sup>12</sup>

## METHODS

### TRIAL DESIGN AND OVERSIGHT

We enrolled patients at 129 sites worldwide from January 2007 through January 2009. Eligible persons were from 18 to 50 years of age, with a diagnosis of ADPKD (see the Supplementary Appendix, available with the full text of this article at NEJM.org),<sup>13</sup> a total kidney volume of 750 ml or more<sup>14,15</sup> as measured with the use of magnetic

resonance imaging (MRI), and a creatinine clearance of 60 ml per minute or more as estimated by means of the Cockcroft–Gault formula.<sup>16</sup> Randomization was carried out centrally, with patients randomly assigned in a 2:1 ratio to receive tolvaptan or placebo and with stratification according to hypertension status (present vs. absent), creatinine clearance ( $<80$  vs.  $\geq 80$  ml per minute), total kidney volume ( $<1000$  vs.  $\geq 1000$  ml), and geographic area.<sup>12</sup>

Tolvaptan dosing was started in daily morning and afternoon doses of 45 mg and 15 mg, respectively, with weekly increases to 60 mg and 30 mg and then to 90 mg and 30 mg, according to patient-reported tolerability. For 36 months, patients took the highest dose that they reported as tolerable. Patients who reported that they could not tolerate the lowest dose were asked to continue follow-up by telephone. Adherence to treatment was self-reported and confirmed by means of pill counts. The use of diuretics and drugs inhibiting the cytochrome P-450 enzyme CYP3A4 was avoided, given their effects on urine output and tolvaptan blood levels, respectively.

The institutional review board or ethics committee at each site approved the protocol; written informed consent was obtained from all participants. A steering committee of investigators and representatives of the sponsor, Otsuka Pharmaceuticals, oversaw the trial design and conduct with the assistance of the independent data and safety monitoring committee and the clinical event committee. The sponsor collected and analyzed the data. The first author assumes responsibility for the overall content and integrity of the manuscript, with substantial contributions from the coauthors, who all had access to the data and jointly decided to submit the manuscript for publication. All authors vouch for the accuracy and completeness of the reported data, as well as the fidelity of this report to the protocol. The protocol is available at NEJM.org and has been published previously.<sup>12</sup>

### TRIAL ASSESSMENTS

Evaluations were performed at baseline, at randomization, weekly during the dose-escalation phase, every 4 months (monthly in Japan) during treatment, and twice between 1 and 6 weeks (with the visits at least 1 week apart) after the completion of treatment at 36 months. Evaluations included

physical examination, assessment of vital signs, electrocardiography, and blood and urine tests. The serum creatinine level was measured centrally with the use of the IDMS-traceable Roche enzymatic method and was reported to two decimal points.<sup>17</sup> Standardized MRI scans of the kidneys were obtained, as described in the protocol, at baseline and at months 12, 24, and 36 ( $\pm 2$  weeks); for patients who did not complete the study, the final MRI scans were obtained within 2 weeks before or after withdrawal if they had not been acquired during the previous 6 months.

#### OUTCOME MEASURES

The primary end point was the annual rate of percentage change in total kidney volume. The composite secondary end point was the time to investigator-assessed clinical progression, defined as worsening kidney function (a 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least 2 weeks); clinically significant kidney pain necessitating medical leave, pharmacologic treatment (narcotic or last-resort analgesic agents), or invasive intervention; worsening hypertension (changes in blood-pressure category, as defined in the protocol, or worsening of hypertension requiring an increase in hypertensive treatment); and worsening albuminuria (according to sex-specified categories as defined in the protocol). These events were further adjudicated by an independent clinical events committee for a sensitivity analysis.

The next secondary end point was the change in the slope of kidney function as measured by the reciprocal of the serum creatinine level.<sup>18</sup> The reciprocal of the serum creatinine level has a linear relationship with the GFR, unlike the serum creatinine level, which has a curvilinear relationship. These values, expressed as (mg per milliliter)<sup>-1</sup>, approximate GFR values, with which clinicians are familiar. Other secondary end points are outlined in the protocol<sup>12</sup> and in the Supplementary Appendix. Equations from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) that are adjusted for ethnic group were used to determine the estimated GFR.<sup>17,19</sup> Kidney-function end points were analyzed during treatment, with the use of measurements obtained at the end of the dose-escalation period and at the last

treatment visit, since tolvaptan reversibly increases the serum creatinine level.<sup>11,20,21</sup> Sensitivity analyses that included data obtained before and after treatment were used to confirm the results obtained during treatment.

#### STATISTICAL ANALYSIS

Using Lefante's formula,<sup>22</sup> we calculated that we would need to enroll 600 patients, assuming standard deviations for total noise and the slope across patients of 0.017 and 0.018 (in  $\log_{10}$  scale), respectively; an average untreated increase in the growth rate for total kidney volume of 7%; 85% power to detect a 20% reduction in the rate of growth; a two-sided alpha level of 0.045; and a 20% withdrawal rate. We doubled this estimated sample size, for a target enrollment of 1200 to 1500 patients, to provide robust statistical power for the primary and composite secondary end points in a single trial.

Details of the analysis are available in the protocol.<sup>12</sup> For the analysis of the primary end point, we compared individual slopes for total kidney volume between the groups, by fitting the  $\log_{10}$ -transformed data on total kidney volume to a linear mixed-effects Laird-Ware model.<sup>23</sup> Antilog (with a base of 10) of the treatment effect and 95% confidence intervals derived from the model (in a  $\log_{10}$  scale) provide a ratio of geometric means of the slope of total kidney volume (i.e., 100% plus annual percentage change). A mixed-model repeated-measures analysis was applied to the repeated measures of change from baseline in  $\log_{10}$ -transformed data on total kidney volume as a sensitivity analysis.

The analysis of the composite secondary end point was performed with the use of the Andersen-Gill approach for the extended Cox model, for analysis of time to multiple events. The P value was provided by the Wald test with the use of a sandwich estimate of the covariance matrix. Treatment was the sole variable in the model.<sup>24</sup> Data were censored when patients withdrew from the trial. The analysis of the slope of kidney-function decline was similar to the analysis of the slope of the total kidney volume.

The primary analyses of all efficacy end points were prespecified as intention-to-treat analyses of data obtained during the treatment period, with sensitivity analyses that included pretreatment and post-treatment data in the intention-to-treat pop-

ulation. Study end points were ordered hierarchically and tested sequentially with the use of gate-keeping procedures. For informational purposes, confidence intervals and P values are provided for subsequent comparisons and sensitivity analyses.

## RESULTS

### PATIENTS

We screened 2122 patients, of whom 1445 were randomly assigned to either tolvaptan (961 patients) or placebo (484, with 1 patient withdrawing after randomization and before receiving any study medication) (Fig. 1). Overall, 1157 patients (80.1%) completed the 3-year trial (77.0% of the patients in the tolvaptan group [2335 exposure-years] and 86.2% of those in the placebo group [1306 exposure-years]). Nearly half the patients who permanently discontinued the study drug — 46% in the tolvaptan group and 40% in the placebo group — agreed to telephone follow-up. The primary efficacy analysis included 1307 of the 1445 patients (90.4%), with 138 patients excluded because of early withdrawal and a lack of measurable follow-up MRI scans. All 1445 patients (100%) were included in the key secondary efficacy analysis, and 1444 (99.9%) were included in the key secondary safety analysis. Demographic and baseline characteristics in the two groups were well balanced (Table 1).

### ADHERENCE TO TREATMENT

Adherence exceeded 90% in 845 of the 961 patients in the tolvaptan group (88%), with an average dose of 95 mg per day, and in 451 of the 483 patients in the placebo group (93%), with an average sham dose of 110 mg per day. Of the patients who completed 36 months of treatment with tolvaptan, 404 (55%) took the high dose (a total daily dose of 120 mg), whereas 157 (21%) and 179 (24%) took the middle dose (90 mg) and low dose (60 mg), respectively. Of the patients who completed 36 months of placebo treatment, 348 (83%), 38 (9%), and 32 (8%) took the corresponding sham doses.

### PRIMARY END POINT

Over the 3-year period, total kidney volume increased by 2.8% per year (95% confidence interval [CI], 2.5 to 3.1) with tolvaptan versus 5.5% per year (95% CI, 5.1 to 6.0) with placebo. Tolvaptan changed the rate of growth by  $-2.7$  percentage

points per year (95% CI,  $-3.3$  to  $-2.1$ ); the ratio of the geometric means of growth rate was 0.97 (95% CI, 0.97 to 0.98;  $P<0.001$ ) (Fig. 2A).

The mixed-model repeated-measures analysis confirmed the analysis of the primary end point (least-squares mean change in total kidney volume over the 3-year period, 9.56% with tolvaptan vs. 18.75% with placebo). This difference of  $-9.2$  percentage points (95% CI,  $-11.1$  to  $-7.3$ ;  $P<0.001$ ) represents a treatment effect of 49.2% in the intention-to-treat population, with a larger effect observed during the first year than during the second and third years (Tables S1 and S2 and Fig. S1 in the Supplementary Appendix). This same analysis, when restricted to patients who were taking the trial drug at the time of image acquisition, showed a higher between-group difference during the third year (Tables S1 and S2 and Fig. S1 in the Supplementary Appendix).

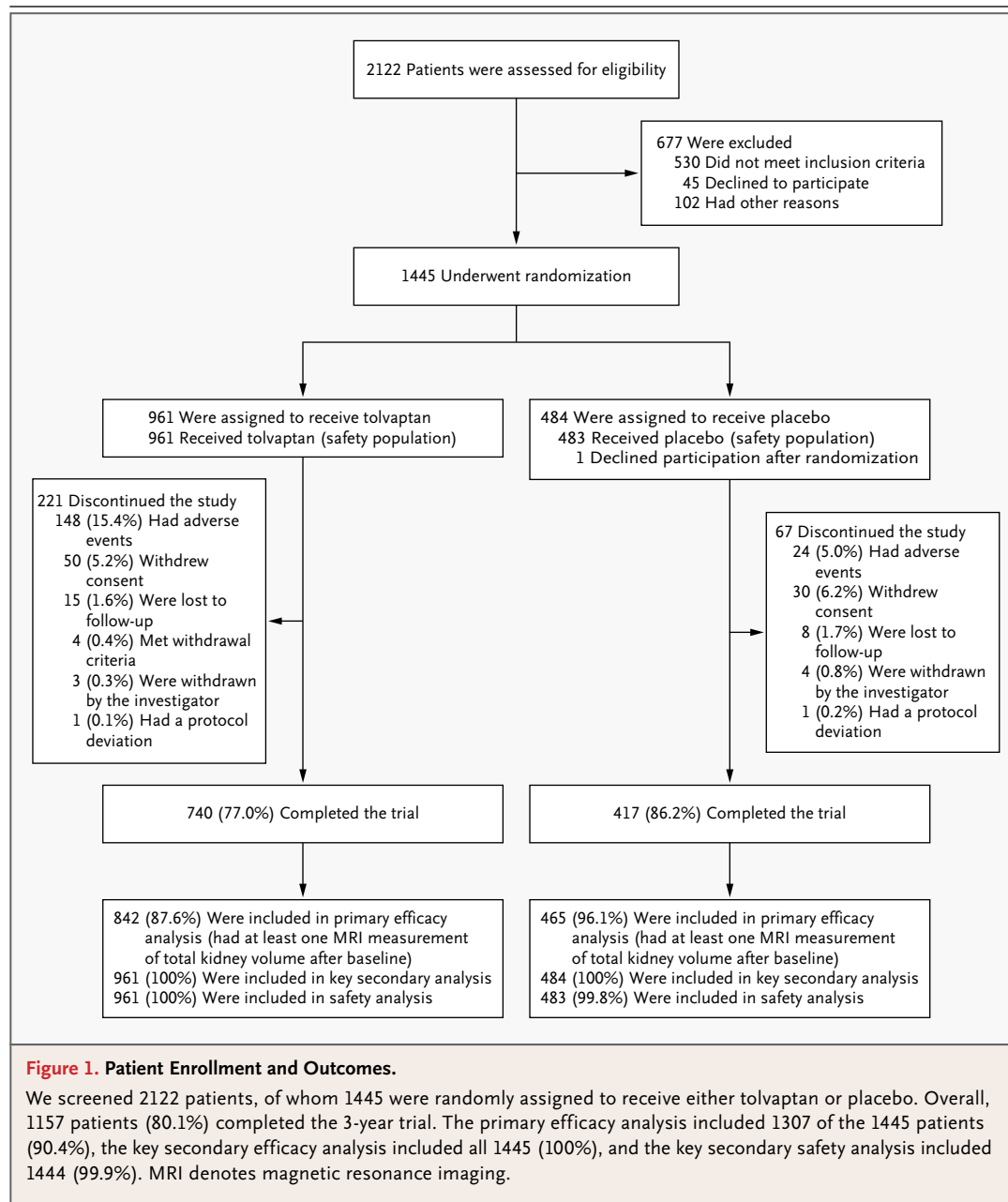
Prespecified subgroup analysis showed that tolvaptan had a beneficial effect on total kidney volume in all subgroups, with patients stratified according to sex, age ( $<35$  years vs.  $\geq 35$  years), total kidney volume at baseline ( $<1500$  ml vs.  $\geq 1500$  ml), estimated creatinine clearance level at baseline ( $<80$  ml per minute vs.  $\geq 80$  ml per minute), and hypertension status (absent vs. present) (Fig. 2B).

### SECONDARY END POINTS

#### *Slope of Kidney Function*

The first noncomposite secondary end point, the slope of kidney function (as assessed by means of the reciprocal of the serum creatinine level) from the end of dose escalation to month 36, also favored tolvaptan, with a slope of  $-2.61$  (mg per milliliter) $^{-1}$  per year, as compared with  $-3.81$  (mg per milliliter) $^{-1}$  per year with placebo; the treatment effect was an increase of 1.20 (mg per milliliter) $^{-1}$  per year (95% CI, 0.62 to 1.78;  $P<0.001$ ) (Fig. 2C). This treatment effect was confirmed by comparing data from pretreatment baseline and post-treatment visits, which showed an increase of 4.93 (mg per milliliter) $^{-1}$  over the 3-year period for tolvaptan, as compared with placebo ( $P<0.001$ ). This corresponds to an increase in the mean serum creatinine level from 1.05 mg per deciliter (93  $\mu$ mol per liter) to 1.21 mg per deciliter (107  $\mu$ mol per liter) in the tolvaptan group, as compared with an increase from 1.04 mg per deciliter (92  $\mu$ mol per liter) to 1.27 mg per deciliter (112  $\mu$ mol per





liter) in the placebo group (mean difference,  $-0.09$  mg per deciliter [ $-8$   $\mu$ mol per liter]; 95% CI,  $-0.13$  to  $-0.06$  [ $-11$  to  $-5$ ];  $P < 0.001$ ).

The mixed-model repeated-measures analysis showed a significant benefit of tolvaptan beginning at year 1 (between-group difference,  $2.02$  [mg per milliliter] $^{-1}$ ;  $P < 0.001$ ) and increasing through year 3 (between-group difference,  $3.68$  [mg per milliliter] $^{-1}$ ;  $P < 0.001$ ) (Table S3 in the Supple-

mentary Appendix). Analysis of the annual estimated GFR slope gave results similar to those of the slopes of the reciprocal of the serum creatinine level, with an estimated GFR slope of  $-2.72$  ml per minute per  $1.73$   $m^2$  per year in the tolvaptan group versus  $-3.70$  in the placebo group (treatment effect, an increase of  $0.98$  ml per minute per  $1.73$   $m^2$  per year; 95% CI,  $0.60$  to  $1.36$ ;  $P < 0.001$ ) (Fig. S3 in the Supplementary Appendix).

Prespecified subgroup analysis suggested that tolvaptan had a beneficial effect on renal function in all stratification subgroups (Fig. 2D). However, these effects were nominally greater among patients 35 years of age or older and among those with hypertension or a total kidney volume of 1500 ml or more.

#### Clinical Progression

Analysis of the key secondary composite end point, tested after the primary end point, showed fewer ADPKD-related events per 100 person-years of follow-up with tolvaptan than with placebo (44 vs. 50 events; hazard ratio, 0.87; 95% CI, 0.78 to 0.97;  $P=0.01$ ) (Fig. 3A and 3B). This result was confirmed by the analysis of time to first event, with a hazard ratio of 0.83 (95% CI, 0.72 to 0.94;  $P=0.005$ ). An analysis of adjudicated events con-

firmed these results (hazard ratio, 0.85; 95% CI, 0.76 to 0.95;  $P=0.004$ ). The outcome of the composite end point was driven by effects on kidney-function decline (2 events per 100 person-years of follow-up in the tolvaptan group vs. 5 in the placebo group; hazard ratio, 0.39; 95% CI, 0.26 to 0.57;  $P<0.001$ ) (Fig. 3C) and kidney pain (5 events per 100 person-years of follow-up in the tolvaptan group vs. 7 in the placebo group; hazard ratio, 0.64; 95% CI, 0.47 to 0.89;  $P=0.007$ ) (Fig. 3D). No effect of treatment was detected with regard to hypertension or albuminuria events (Fig. 3A, and Fig. S2 in the Supplementary Appendix).

#### Other Secondary End Points

After the first three sequentially tested end points, all other prespecified end points did not differ significantly between the tolvaptan group and

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.\***

Characteristic	Tolvaptan (N=961)	Placebo (N=484)
Male sex — no. (%)	495 (51.5)	251 (51.9)
Age — yr	39±7	39±7
Race — no. (%)†		
White	810 (84.3)	408 (84.3)
Asian	121 (12.6)	62 (12.8)
Other	30 (3.1)	14 (2.9)
Stratification factor — no. (%)		
Hypertension	765 (79.6)	382 (78.9)
Estimated creatinine clearance <80 ml/min	242 (25.2)	130 (26.9)
Total kidney volume <1000 ml	197 (20.5)	101 (20.9)
Medical history — no. (%)		
Hematuria	338 (35.2)	164 (33.9)
Kidney pain	496 (51.6)	239 (49.4)
Nephrolithiasis	187 (19.5)	109 (22.5)
Urinary tract infection	290 (30.2)	164 (33.9)
Anemia	105 (10.9)	48 (9.9)
Proteinuria	233 (24.2)	116 (24.0)
Current medication — no. (%)		
Angiotensin-converting-enzyme inhibitor	419 (43.6)	199 (41.1)
Angiotensin-receptor blocker	307 (31.9)	165 (34.1)
Angiotensin-converting-enzyme inhibitor, angiotensin-receptor blocker, or both	683 (71.1)	350 (72.3)
Beta-blocker	171 (17.8)	94 (19.4)
Calcium-channel blocker	180 (18.7)	104 (21.5)
Diuretic	32 (3.3)	14 (2.9)



**Table 1. (Continued.)**

Characteristic	Tolvaptan (N=961)	Placebo (N=484)
Height — cm	173.5±10.4	173.6±7.8
Weight — kg	79±18	79±18
Blood pressure — mm Hg		
Systolic	128.6±13.5	128.3±13.5
Diastolic	82.5±9.9	82.5±9.3
Total kidney volume — ml	1705±921	1668±873
Height-adjusted total kidney volume — ml/m	979±515	958±483
Serum creatinine — mg/dl‡	1.05±0.30	1.04±0.32
Reciprocal of serum creatinine — (mg/ml) <sup>-1</sup>	102.27±27.21	104.30±35.60
Estimated creatinine clearance — ml/min§	104.08±32.76	103.80±35.60
Estimated GFR — ml/min/1.73 m <sup>2</sup> ¶	81.35±21.02	82.14±22.73
Urinary albumin-to-creatinine ratio	7.2±14.3	8.6±21.7

\* Plus-minus values are means ±SD. No significant between-group differences were found for any of the baseline characteristics. GFR denotes glomerular filtration rate.

† Race was self-reported.

‡ To convert values for creatinine to micromoles per liter, multiply by 88.4.

§ The estimated creatinine clearance was measured with the use of the Cockcroft–Gault formula.

¶ Estimated GFR was measured with the use of the Chronic Kidney Disease Epidemiology Collaboration equation adjusted for race.

|| For the urinary albumin-to-creatinine ratio, albumin was measured in milligrams per deciliter and creatinine in millimoles per deciliter.

the placebo group (Table S4 in the Supplementary Appendix).

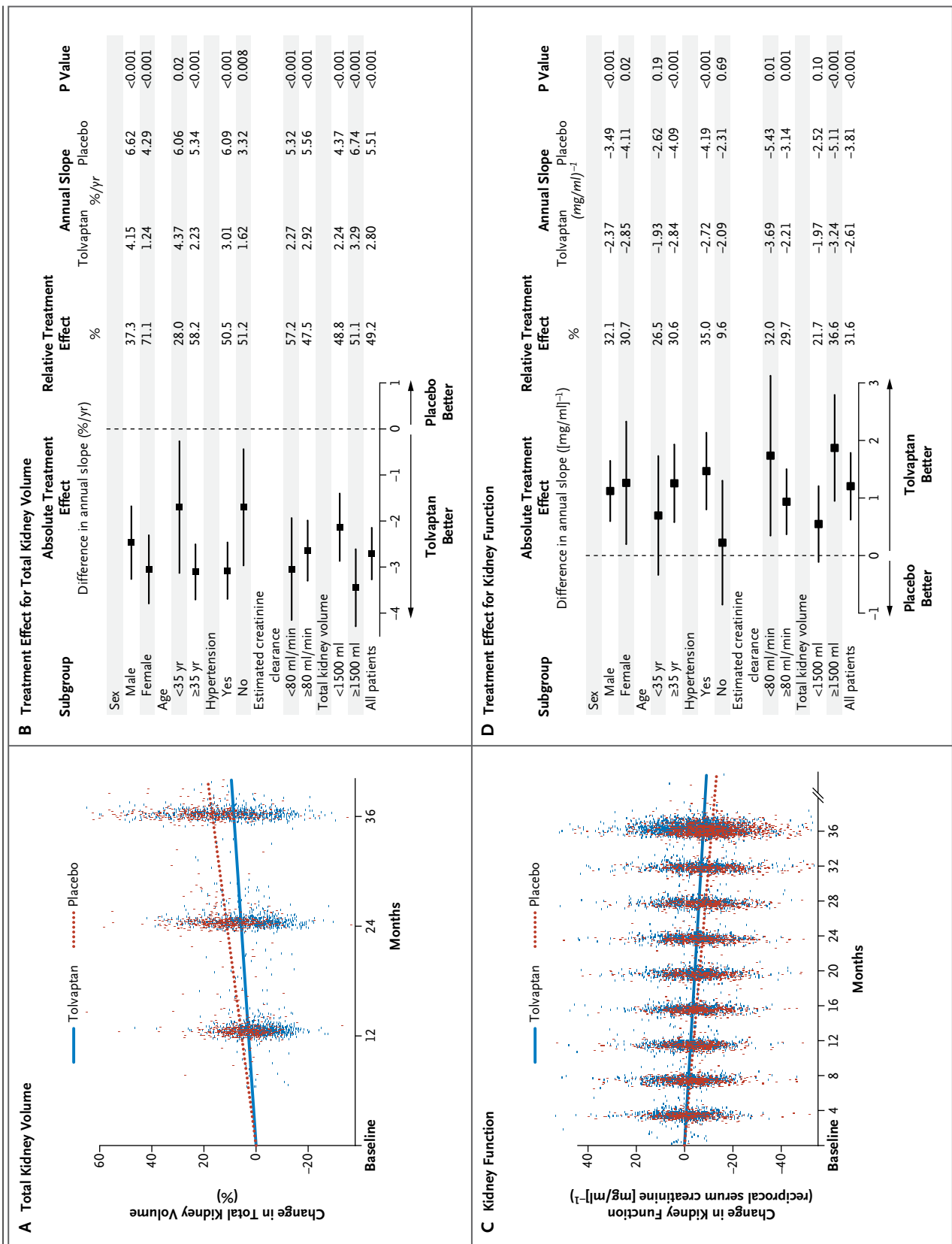
#### ADVERSE EVENTS

The rates of adverse events were similar in the tolvaptan group (97.9% of patients) and the placebo group (97.1%). Patients who received tolvaptan had a higher frequency of adverse events related to increased aquaresis (thirst, polyuria, nocturia, and polydipsia, as a result of the excretion of electrolyte-free water), whereas those who received placebo had higher frequencies of adverse events related to ADPKD (kidney pain, hematuria, urinary tract infection, and back pain) (Table 2, and Table S5 in the Supplementary Appendix). Serious adverse events occurring in at least 0.5% of the patients in either group are summarized in Table 2. A greater proportion of patients who received tolvaptan had elevations of liver-enzyme levels. Serious adverse events associated with chest pain and headache were slightly more frequent in the tolvaptan group, but the only two episodes of myocardial infarction and the only episode of subarachnoid hemorrhage occurred in the placebo group. No patients died during the trial.

A total of 23.0% of the patients who received tolvaptan and 13.8% of those who received placebo permanently discontinued the trial drug. Adverse events led to more discontinuations in the tolvaptan group than in the placebo group (15.4% of patients vs. 5.0%) (Fig. 1). Of the 961 patients in the tolvaptan group, 8.3% and 1.2% discontinued the trial drug because of aquaresis-related symptoms and liver-function abnormalities, respectively.

#### LABORATORY AND CLINICAL DATA

Laboratory studies are summarized in Table S6 in the Supplementary Appendix. Treatment with tolvaptan resulted in an increase in the mean serum sodium level of less than 2.5 mmol per liter by the end of the dose-escalation period. This reached potentially clinically important levels (defined as a value >150 mmol per liter at any visit) in 4.0% of the patients who received tolvaptan and in 1.4% of those who received placebo. Despite an increase in serum uric acid levels and in the frequency of gout among patients in the tolvaptan group, as compared with those in the placebo group (2.9% vs. 1.4%), these events were not con-



**Figure 2 (facing page). Effect of Tolvaptan on the Annual Slopes of Total Kidney Volume and Kidney Function.**

The slopes of the growth in total kidney volume in the intention-to-treat population during the 3-year treatment period are shown, with individual patient data included in the slope calculations; 6 outliers of the 1315 data points in the placebo group and 3 outliers of the 2370 data points in the tolvaptan group are not shown. The ratio of the geometric mean was 0.97 (95% CI, 0.97 to 0.98;  $P < 0.001$ ) (Panel A). The forest plot of the treatment effect according to baseline subgroups was based on the between-group difference in the slopes, with the variance approximated by means of the delta method under the assumption of independence between the slopes. Horizontal bars indicate 95% confidence intervals (Panel B). The slopes of kidney function were estimated with the use of the reciprocal of the serum creatinine level in the intention-to-treat population during the treatment period, and individual patient data were included in the slope calculations; 19 outliers of 4759 data points in the placebo group and 16 outliers of 8564 data points in the tolvaptan group are not shown. The annual difference in slope was 1.202 (mg per milliliter)<sup>-1</sup> per year (95% CI, 0.62 to 1.78;  $P < 0.001$ ) (Panel C). The forest plot of the treatment effect for kidney function according to the baseline subgroups was based on the difference in the annual change in slope (with 95% confidence intervals) of the reciprocal of the serum creatinine level (Panel D).

sidered to be severe, nor did they lead to serious adverse events or withdrawal from the trial.

More patients who received tolvaptan than those who received placebo (4.9% vs. 1.2%) had potentially clinically important elevations of alanine aminotransferase, defined as a value that was more than 2.5 times the upper limit of the normal range at any trial visit. Fewer patients who received tolvaptan than those who received placebo (0.9% vs. 1.9%) had potentially clinically important increases in the bilirubin level, defined as a value that was more than 1.5 times the upper limit of the normal range. A review of central and local laboratory data from narrative reports of serious adverse events and events leading to withdrawal from the study identified two patients in the tolvaptan group who had concurrent elevations in the alanine aminotransferase or aspartate aminotransferase level (>3 times the upper limit of the normal range) and the bilirubin level (>2 times the upper limit of the normal range). In all cases, the abnormalities either resolved during treatment or returned toward baseline values with drug interruption or withdrawal. No reports of persistent sequelae were received. There were no sig-

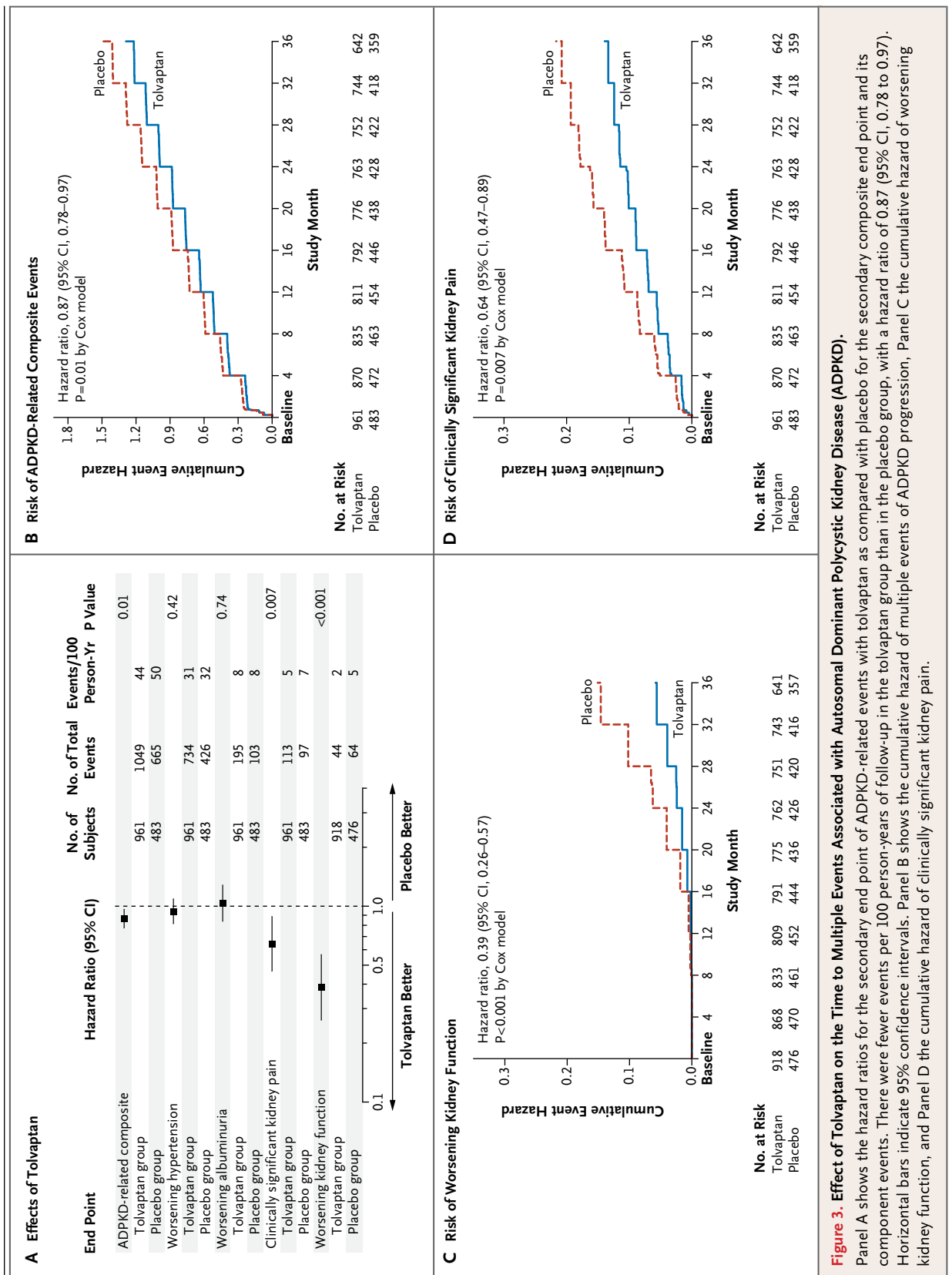
nificant differences in mean body weight, systolic or diastolic blood pressure, or heart rate between the patients who received tolvaptan and those who received placebo.

## DISCUSSION

The administration of tolvaptan for 36 months was associated with slowed kidney growth and functional decline and with a reduced frequency of ADPKD-related complications among patients with a large kidney volume but a relatively preserved GFR. The change in total kidney volume with tolvaptan, as compared with placebo, was more pronounced in the first year of treatment. An acute decrease in the secretion of cyst fluid probably contributed to this effect; this hypothesis is supported by short-term trials of tolvaptan in which a 3 to 4% reduction in total kidney volume was observed at 1 to 3 weeks.<sup>20,21</sup> The steadily accumulating benefit observed with tolvaptan in years 2 and 3 is consistent with the inhibition of cyst-cell proliferation, as shown in animal and ex vivo human models.<sup>3-6,25</sup> The beneficial effect of tolvaptan on kidney growth was observed in all subgroups.

The complications of ADPKD depend on the number, size, and location of cysts. A large total kidney volume has been associated with hypertension, gross hematuria, nephrolithiasis, and pain in many cross-sectional and longitudinal studies.<sup>26</sup> The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) showed that total kidney volume as measured with the use of MRI predicts functional decline and morbidity, supporting its use as a clinically relevant marker of progression at early stages of disease.<sup>14,15</sup> Nevertheless, the use of total kidney volume as a surrogate for treatment efficacy has been questioned.<sup>27</sup>

We evaluated the effects of tolvaptan on a composite end point of clinically relevant outcomes and observed a reduction in events of worsening kidney function and kidney pain. The decrease in kidney pain occurred early and throughout treatment, possibly reflecting a rapid effect on fluid secretion and intracystic pressure,<sup>20,21,25</sup> whereas the effect on kidney function became evident later, given the time required for a patient to have a 25% reduction in the reciprocal of the serum creatinine level. The effect on kidney function was nominally greater among patients 35 years of age or older and among those with hyperten-



sion or a total kidney volume of 1500 ml or more at baseline — that is, among patients with more advanced disease, who were more likely to have functional decline during the relatively short duration of the trial, which is consistent with the results of the CRISP study.<sup>15</sup>

Whether tolvaptan is a helpful long-term treatment in patients with ADPKD will depend on a balance between benefits and risks. Adverse events consistent with the natural history of ADPKD were more frequent among patients who received placebo than among those who received tolvaptan. Some adverse events more common in the tolvaptan group were consistent with its aquaretic effect. Aquaresis-related adverse events led to the discontinuation of tolvaptan in approximately 8% of participants, mostly within the first month. Adverse events related to aquaresis in previous clinical trials of tolvaptan for hyponatremia or heart failure were similar to those observed in the current trial, but the higher frequency of liver-enzyme elevations was not observed in the previous trials.<sup>28-31</sup>

This trial has several limitations. Patients were asked to maintain good hydration and avoid thirst. In fact, a substantial number of patients in the placebo group reported polyuria (17.2%) and nocturia (13.0%). Although maintaining hydration helped ensure that the blinding in the study was maintained, the suppression of vasopressin release in the placebo group may have led to an underestimation of the beneficial effect of tolvaptan and may account for the lower rates of kidney growth observed in the placebo group in the current trial, as compared with the rates in the control groups of previous ADPKD trials (6.8 to 11.8% per year).<sup>27,32-36</sup> Although patients with near-normal kidney function were included in the study, hypertension had already developed in most of these patients at baseline, limiting the ability to detect a potential beneficial effect of tolvaptan on the development or progression of hypertension.

In conclusion, tolvaptan, when given over a period of 3 years, slows the increase in total kidney volume and the decline in kidney function in patients with ADPKD. The potential benefit is not without risks. Thirst, polyuria, and related adverse events may affect the ability of some patients to take effective doses of tolvaptan. The potential effects on liver-enzyme levels and plasma levels of sodium and uric acid require monitoring.

**Table 2. Most Common Adverse Events and Serious Adverse Events.\***

Event	Tolvaptan (N=961)	Placebo (N=483)
<i>no. of patients with event (%)</i>		
<b>Adverse events more common in tolvaptan group</b>		
Thirst	531 (55.3)†	99 (20.5)
Polyuria	368 (38.3)†	83 (17.2)
Nocturia	280 (29.1)†	63 (13.0)
Headache	240 (25.0)	120 (24.8)
Pollakiuria‡	223 (23.2)†	26 (5.4)
Dry mouth	154 (16.0)	59 (12.2)
Diarrhea	128 (13.3)	53 (11.0)
Fatigue	131 (13.6)	47 (9.7)
Dizziness	109 (11.3)	42 (8.7)
Polydipsia	100 (10.4)†	17 (3.5)
<b>Adverse events more common in placebo group</b>		
Hypertension	309 (32.2)	174 (36.0)
Renal pain	259 (27.0)§	169 (35.0)
Nasopharyngitis	210 (21.9)	111 (23.0)
Back pain	132 (13.7)	88 (18.2)
Increased creatinine level	135 (14.0)	71 (14.7)
Hematuria	75 (7.8)†	68 (14.1)
Urinary tract infection	80 (8.3)§	61 (12.6)
Nausea	98 (10.2)	57 (11.8)
<b>Serious adverse events more common in tolvaptan group</b>		
Alanine aminotransferase elevation	9 (0.9)	2 (0.4)
Aspartate aminotransferase elevation	9 (0.9)	2 (0.4)
Chest pain	8 (0.8)	2 (0.4)
Headache	5 (0.5)	0
<b>Serious adverse events more common in placebo group</b>		
Pyelonephritis	5 (0.5)	5 (1.0)
Renal-cyst infection	6 (0.6)	4 (0.8)
Renal-cyst hemorrhage	3 (0.3)	4 (0.8)
Renal pain	1 (0.1)	4 (0.8)
Appendicitis	1 (0.1)	4 (0.8)
Nephrolithiasis	2 (0.2)	3 (0.6)
Urinary tract infection	1 (0.1)	3 (0.6)
Hypertension	1 (0.1)	3 (0.6)

\* Adverse events were categorized according to the *Medical Dictionary for Regulatory Activities* (MedDRA).

† P<0.001 by Fisher's exact test, as compared with the placebo group.

‡ Pollakiuria is more commonly called urinary frequency.

§ P<0.05 by Fisher's exact test, as compared with the placebo group.



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